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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,794	08/21/2001	Melvyn Little	31304-756.831	5254

21971 7590 04/12/2006

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EXAMINER	
TUNGATURTHI, PARITHOSH K	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 04/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/674,794	LITTLE ET AL.	
	Examiner	Art Unit	
	Parithosh K. Tungaturthi	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-31* is/are pending in the application.

4a) Of the above claim(s) *30 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants response to the office action filed on 02/03/2006 is acknowledged.

2. Claims 1-25 are cancelled.

3. Claims 26-31 have been newly added.

4. Claims 26-29 are drawn to a bispecific tetravalent homodimeric antibody, and Claims 30 and 31 are drawn to a method of producing said single-chain Fv monomer. Thus, claims "26-29" and "30-31" comprise separate inventions because the product of claims "26-29" can be produced by materially different process in addition to the materially different methods of claims "30-31" (please see the restriction requirement mailed on 06/10/2005). Since the applicant elected the group drawn to the product claims in the previous office action (please see the applicants response filed 08/02/2005), only claims 26-29 are examined in the current office action.

5. Claims 26-29 are under examination.

6. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior office action.

7. This office action consists of New Grounds of Rejection.

Rejections Withdrawn

8. The rejection of Claims 1-11, 20 and 21 under 35 U.S.C. 112, first paragraph is withdrawn in view the amendments to the claims (the claims have been cancelled).

9. The rejection of claims 1-11 and 20-21 under 35 U.S.C. 103(a) as being unpatentable over Mezes et al (U.S. Patent 5,892,020; Filed: June 7th, 1995) in view of Hollinger et al (U.S. Patent 5837242; Filed December 3rd, 1993) and Pastan et al (U.S. Patent 5,635,599; Issued June 3rd, 1997) and Whitlow et al (U.S. Patent 5,856,456; Filed April 7th, 1994) and Coloma and Morrison (Nature Biotechnology 1997 Vol. 15:15-163; IDS – 08.21.05) is withdrawn in view the amendments to the claims (the claims have been cancelled).

This Application Consists of New Grounds of Rejection

10. The newly added claims, claims 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hollinger et al (U.S. Patent 5837242; Filed December 3rd, 1993) in view of Whitlow et al (U.S. Patent 5,856,456; Filed April 7th, 1994) and further in view of Csoka et al (Leukemia, 1996. 10:1765-1772).

The instant claims are drawn to a bispecific tetravalent homodimeric Fv antibody formed by two single-chain Fv monomers, each of said Fv monomers having at least four variable domains, wherein said four variable domains are V_H-A, V_L-A, V_H-B and V_LB, wherein V_H-A and V_L-A are V_H and V_L domains of an antibody specific for antigen A, respectively, and V_H-B and V_L-B are V_H and V_L domains of an antibody specific for antigen B, respectively; V_H-A is linked to V_L--B by peptide linker 1, V_L-B is linked to V_H-B by peptide linker 2, V_H-B is linked to V_L-A by peptide linker 3; and said peptide linker 1 and said peptide linker 3 are a peptide bond or have about 1 to about 10 amino acids;

and said peptide linker 2 has 3 to about 10 amino acids, wherein said peptide linker 1 and peptide linker 2 have the amino acid sequence GG, wherein said peptide linker 2 comprises the amino acid sequence GGPGS and wherein the antibody is bispecific for human CD3 and CD19.

Hollinger et al teach (paragraphs 62-64, in particular) a bispecific dimer consisting of a first polypeptide comprising a first domain which comprises a binding region of an immunoglobulin heavy chain variable region, and a second domain which comprises a binding region of an immunoglobulin light chain variable region, the domains of the first polypeptide being linked but incapable of associating with each other to form an antigen binding site; and (ii) a second polypeptide which has a first domain, which comprises a binding region of an immunoglobulin heavy chain variable region, a second domain, which comprises a binding region of an immunoglobulin light chain variable region, and a polypeptide linker linking the first and second domains such that the fusion polypeptide can be arranged as VH_A-VH_B-VL_B-VH_A (figure 7, in particular). Hollinger et al further teach the diabody dimers wherein, there is a possibility of making $(Fab)_2$ like fragments with four binding specificities, or two binding specificities (but two binding sites for each), or a single binding specificity (but four copies of each; and that such diabody-dimers could have enhances avidity of binding compared with $(Fab)_2$ fragments (paragraph 64, in particular). Hollinger et al teach that the domains of the polypeptide are linked by a peptide linker, the linker may be "short", consisting of a too few amino acids to allow the VL domain of a chain to combine with

the VH domain of that chain. This may be less than 10 amino acids, most preferably, 5, 4, 3, 2, or 1. It may be in certain cases that 9, 8, 7 or 6 amino acids are suitable (paragraph 29, in particular). Hollinger et al also suggested that one should choose antibodies for which the VH and VL domains are known to associate and form a stable FV fragment in analogy to the diabody design using short linkers (5 residues) to prevent the VH and VL domains on the same chain from pairing with each other (paragraph 70, in particular). Hollinger et al also teach the construction of a diabody using "two glycine residues" as a linker (example 15, in particular).

Whitlow et al (U.S. Patent 5,856,456) teach that a novel peptide linker comprising the amino acid sequence from about 2 to about 20 having a first end connected to a first protein domain, and having a second end connected to a second protein domain, wherein the peptide comprises at least one proline residue within the sequence, the proline being position next to a charged amino acid, and the charged amino acid-proline pair is positioned within the peptide linker to inhibit proteolysis of said polypeptide. (column 4 lines 33-44, in particular). Whitlow et al also teach a novel peptide linker comprising the amino acid sequence: U_mXPZ_n wherein U and Z can be single amino acids, such that n and m are any integers from 0 to 48 and n+m is not greater that 48, and X is a charged amino acid.

Csoka et al teach (please see entire article) a CD3xCD19 bispecific antibody that facilitates both stimulation of resting PBMC to fully activated cytotoxic T lymphocytes without the requirement of additional external costimulatory signals and specific targeting of these preactivated T lymphoblasts to autologous leukemic cells by the same

CD3xCD19 bsAb. Csoka et al teach (please see discussion, in particular) the resting T cells can sufficiently be activated by incubation with relatively low amounts of the CD3xCD19 bispecific antibody without further external costimulatory signals, and that the preactivated T cells are able to specifically lyse autologous Acute Lymphoblastic Leukemia blasts only in the presence of CD3xCD19 bispecific antibody but not with CD3 and CD19 parental antibody at the same concentration. Csoka et al also teach that the adjuvant immunotherapy using CD3xCD19 bispecific antibodies might be beneficial for patients relapsed and/or therapy-resistant common Acute Lymphoblastic Leukemia.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have generated a bispecific tetravalent homodimeric Fv antibody wherein the said peptide linkers have the amino acid sequence GG as taught by as taught by Hollinger et al or the amino acid sequence GGPGS as taught by Whitlow et al, and further wherein the antibody is bispecific for human CD3 and CD19 as taught by Csoka et al.

One of ordinary skill in the art would have been motivated and would have reasonable expectation of success to have generated a bispecific tetravalent homodimeric Fv antibody formed by two single-chain Fv monomers, each of said Fv monomers having at least four variable domains, wherein said four variable domains are V_H-A, V_L-A, V_H-B and V_LB, wherein V_H-A and V_L-A are V_H and V_L domains of an

antibody specific for antigen A, respectively, and V_H-B and V_L-B are V_H and V_L domains of an antibody specific for antigen B, respectively; V_H-A is linked to V_L--B by peptide linker 1, V_L-B is linked to V_H-B by peptide linker 2, V_H-B is linked to V_L-A by peptide linker 3; and said peptide linker 1 and said peptide linker 3 are a peptide bond or have about 1 to about 10 amino acids; and said peptide linker 2 has 3 to about 10 amino acids as taught by Hollinger et al because Hollinger et al teach a bispecific dimer consisting of a first polypeptide comprising a first domain which comprises a binding region of an immunoglobulin heavy chain variable region, and a second domain which comprises a binding region of an immunoglobulin light chain variable region, the domains of the first polypeptide being linked but incapable of associating with each other to form an antigen binding site; and (ii) a second polypeptide which has a first domain, which comprises a binding region of an immunoglobulin heavy chain variable region, a second domain, which comprises a binding region of an immunoglobulin light chain variable region, and a polypeptide linker linking the first and second domains such that the fusion polypeptide can be arranged as VH_A-VH_B-VL_B-VH_A.

In addition, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have generated a bispecific tetravalent homodimeric Fv antibody as claimed because Hollinger et al teach that the domains of the polypeptide are linked by a peptide linker, the linker may be "short", consisting of too few amino acids to allow the VL domain of a chain to combine with the VH domain of that chain, in addition to "two glycine residues" as a linker such that the domains are not allowed to pair with each other, in addition to teaching the diabody

dimers wherein, there is a possibility of making $(Fab)_2$ like fragments with four binding specificities, or two binding specificities (but two binding sites for each), or a single binding specificity (but four copies of each; and that such diabody-dimers could have enhances avidity of binding compared with $(Fab)_2$ fragments.

Further, one of ordinary skill in the art would have known to combine the teachings of Hollinger et al and Whitlow et al because Hollinger teach a diabody arranged in the orientation of VH_A-VH_B-VL_B-VH_A, and a diabody dimer with four binding specificities, or two binding specificities (but two binding sites for each) and introduce the amino acid sequence GGPGS for a linker as taught by Whitlow et al because Whitlow et al teach a novel peptide linker comprising the amino acid sequence from about 2 to about 20 and further because Whitlow et al teach a novel peptide linker comprising the amino acid sequence: U_mXPZ_n wherein U and Z can be single amino acids, such that n and m are any integers from 0 to 48 and n+m is not greater that 48, and X is a charged amino acid.

Furthermore, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have generated a bispecific tetravalent homodimeric Fv antibody for human CD3 and CD19 by combining the teachings of Hollinger et al and Csoka et al, because Hollinger et al teach diabody dimers consisting of $(Fab)_2$ like fragments with four binding specificities, or two binding specificities (but two binding sites for each) which could have enhances avidity of binding compared with $(Fab)_2$ fragments and because Csoka et al teach a CD3xCD19 bispecific antibody that facilitates both stimulation of resting PBMC to fully activated

cytotoxic T lymphocytes without the requirement of additional external costimulatory signals and specific targeting of these preactivated T lymphoblasts to autologous leukemic cells by the same CD3xCD19 bsAb and that the resting T cells can sufficiently be activated by incubation with relatively low amounts of the CD3xCD19 bispecific antibody without further external costimulatory signals, and that the preactivated T cells are able to specifically lyse autologous Acute Lymphoblastic Leukemia blasts only in the presence of CD3xCD19 bispecific antibody but not with CD3 and CD19 parental antibody at the same concentration.

Thus, it would have been obvious to one skilled in the art to combine the teachings of Hollinger et al, Whitlow et al and Csoka et al to generate a bispecific tetravalent homodimeric Fv antibody wherein the said peptide linkers have the amino acid sequence GG or the amino acid sequence GGPGS as taught by Whitlow et al, and further wherein the antibody is bispecific for human CD3 and CD19, because Hollinger et al teach a diabody arranged in the orientation of VH_A-VH_B-VL_B-VH_A, and a diabody dimer with four binding specificities, Whitlow et al teach a linker comprising the amino acid sequence GGPGS and because Csoka et al also teach that the adjuvant immunotherapy using CD3xCD19 bispecific antibodies might be beneficial for patients relapsed and/or therapy-resistant common Acute Lymphoblastic Leukemia.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Response to Applicants Arguments

11. Applicants argue that "Hollinger et al. refer to so-called diabodies.....do not disclose or suggest switching to another antibody format to make a tetravalent bispecific antibody from the same polypeptide chain as claimed in the present application" (see page 6 of the response, in particular). Applicants further argue that Whitlow et al teaches away from the present invention as they disclose that "the requirements for a sFv is that the linker be longer than 12 amino acids (see page 8, in particular).

The above arguments are carefully considered, but are not found persuasive.

In response to the arguments presented in view of the teachings of Hollinger et al, the applicant is respectfully reminded of the teachings of Hollinger et al wherein Hollinger et al teach the diabody (arranged in the orientation of VH_A-VH_B-VL_B-VH_A, which is identical to the orientation claimed) and the diabody dimers which can form $(Fab)_2$ like fragments with four binding specificities, or two binding specificities (but two binding sites for each) (paragraph 64) thus resulting in a tetravalent antibody. Further, the applicant agrees that Hollinger et al teach that the short linker prevents the pairing of the connected two domains (please see page 7 first paragraph of the response).

In addition, the Whitlow et al teaches "as pointed out by the applicant (page 8, second paragraph of the response) a novel peptide linker comprising the amino acid sequence: U_mXPZ_n wherein U and Z can be single amino acids, such that n and m are any integers from 0 to 48 and n+m is not greater that 48, and X is a charged amino acid (please see below for a detailed teaching of Whitlow et al). Further, the claim recites "wherein said peptide linker comprises the amino acid sequence GGPGS". Thus, the claim does not specify the exact length of the linker and hence does not necessarily

mean that the linker is exactly 5 amino acids in length. Since the claim recites "comprises", the teachings of Whitlow et al in regard to the length of the linker is irrelevant and thus read on the claim as written. Thus, Whitlow et al clearly suggest a linker comprising the amino acid sequence GGPGS as claimed.

Hence, the applicants are considered non-persuasive for the reasons stated above and further, the applicant is requested to consider the rejection below for a detailed description of the teachings of the references.

Conclusion

12. No Claims are allowable.

13. **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

15. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
Parithosh K. Tungaturthi Ph.D.
(571) 272-8789

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER